SOLVATES OF CEFPROZIL

Field of the Invention

The field of the invention relates to solvates of cefprozil. The invention also relates to processes for preparing the solvates of cefprozil, crystalline cefprozil from said solvates and pharmaceutical compositions that include the crystalline cefprozil.

Background of the Invention

Cefprozil is a cephalosporin antibiotic for oral administration and is disclosed in U.S. Patent No. 4,520,334. Chemically, cefprozil is 7β[(D)-2-amino-2-(4-hydroxyphenyl) acetamido]-3-(Z)-1-propenyl]-ceph-3-em-4-carboxylic acid. Cefprozil has a broad spectrum of antibacterial activity against both gram-positive and gram-negative organisms. U.S. Patent No. 4,694,079 discloses a crystalline dimethylformamide solvate of cefprozil characterized by a specific powder X-Ray diffraction pattern and its conversion to cefprozil via lyophilization from an aqueous solution.

We have found that cefprozil forms good crystalline solvates with N-methylpyrrolidone and N,N-dimethylacetamide. These solvates are easily crystallized out from the reaction mixture, and their conversion to cefprozil requires very mild conditions yielding pure cefprozil. The solvates serve as useful intermediates for preparing cefprozil.

Accordingly, methods for the total synthesis of these promising compounds and intermediates to these compounds are highly desirable, particularly the methods, which are adaptable to large scale manufacture, and result in pure compounds and reduced cost of manufacture.

Summary of the Invention

In one general aspect, there is provided an N-methylpyrrolidone solvate of cefprozil.

In another general aspect, there is provided an N,N-dimethylacetamide solvate of cefprozil.

In another general aspect there is provided a process for the preparation of the N-methylpyrrolidone solvate of cefprozil. The process includes obtaining a solution of cefprozil in one or more solvents; adding N-methylpyrrolidone at a pH of about 4.5 to about 6.5; and isolating the N-methylpyrrolidone solvate of cefprozil.

In another general aspect there is provided a process for the preparation of the N,N-dimethylacetamide solvate of cefprozil. The process includes obtaining a solution of cefprozil in one or more solvents; adding N,N-dimethylactamide at a pH of about 4.5 to about 6.5; and isolating the N,N-dimethylacetamide solvate of cefprozil.

In another general aspect there is provided a process for the preparation of the crystalline cefprozil from N-methylpyrrolidone solvate or N,N-dimethylacetamide solvate of cefprozil. The process includes obtaining a solution of N-methylpyrrolidone solvate or N,N-dimethylacetamide solvate of cefprozil in one or more solvents; stirring the solution at a temperature of from about 20°C to about 60°C; and isolating the crystalline cefprozil.

The solvent may be one or more of acetonitrile, ketone, alcohol, cyclic ether, water, or mixtures thereof. The ketone may include one or more of acetone and ethylmethyl ketone. The alcohol may include one or more of methanol, ethanol, denatured spirit, propanol, and isopropanol. The cyclic ether may include one or more of dioxane and tetrahydrofuran. Isolating the solvate or crystalline cefprozil includes one or more of filtration, filtration under vacuum, decantation and centrifugation.

The process may include further drying of the product obtained.

In one general aspect, the solution of cefprozil may be obtained by dissolving a salt of cefprozil, or adding a base to a suspension of cefprozil in a solvent. Alternatively, the solution may be obtained directly from the reaction in which cefprozil is formed.

In another general aspect, slurry containing the solvate or crystalline cefprozil may be cooled prior to isolation to obtain better yields and the product may be washed with a suitable solvent.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of a crystalline cefprozil; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have developed new solvates of cefprozil, and in particular, the N-methylpyrrolidone solvate and N, N-dimethylacetamide solvates of cefprozil.

In general, the N-methylpyrrolidone solvate of cefprozil may be characterized by a crystalline structure containing cefprozil and N-methyl pyrrolidone in a molar ratio of 1: 1.5. N-methylpyrrolidone solvate of cefprozil may also be characterized by the X-ray powder diffraction peaks at about 6.24, 6.48 and 18.64 degrees two-theta.

In general, the N,N-dimethylacetamide solvate of cefprozil may be characterized by a crystalline structure containing cefprozil and N,N-dimethylacetamide in a molar ratio of 2:1.5. N,N-dimethylacetamide solvate of cefprozil may also be characterized by X-ray powder diffraction peaks at about 6.48, 7.08, 8.46 and 18.78 degrees two-theta. It may be further characterized by X-ray powder diffraction peaks at about 18.32, 20.06, 21.64, 22.16 and 24.7 degrees two-theta.

The inventors have developed processes for the preparation of the N-methylpyrrolidone and N,N-dimethylacetamide solvates of cefprozil. The inventors also have developed a process for the preparation of a crystalline cefprozil from N-methylpyrrolidone or N,N-dimethylacetamide solvates of cefprozil. The inventors also have developed pharmaceutical compositions that contain the crystalline cefprozil, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In one aspect, the N-methylpyrrolidone solvate of cefprozil is prepared by a process comprising obtaining a solution of obtaining a solution of cefprozil in one or more solvents; adding N-methylpyrrolidone at a pH of about 4.5 to about 6.5; and isolating the N-methylpyrrolidone solvate of cefprozil.

In another aspect, the N,N-dimethylacetamide solvate of cefprozil is prepared by a process comprising obtaining a solution of obtaining a solution of cefprozil in one or more

solvents; adding N,N-dimethylacetamide at a pH of about 4.5 to about 6.5; and isolating the N,N-dimethylacetamide solvate of cefprozil.

In general, the solution of cefprozil may be obtained by dissolving a salt of cefprozil, or adding a base to a suspension of cefprozil in a solvent. Alternatively, such a solution may be obtained directly from the reaction in which cefprozil is formed.

Examples of suitable bases include alkali metal salts of carboxylic acids, such as sodium acetate and potassium acetate; organic amines, such as triethylamine, pyridine, picoline, ethanolamine, triethanolamine, and dicyclohexylamine; ammonium hydroxide; alkali metal hydroxides, such as sodium hydroxide and potassium hydroxide; alkali metal carbonates, such as sodium carbonate and potassium carbonate; and alkali metal bicarbonates such as sodium bicarbonate.

The above bases may also be used for adjusting the pH of the solution of cefprozil to about 4.5 to about 6.5. For example, the pH may range from about 5.5 to about 6.5.

In general, a substantial excess of N-methylpyrrolidone, or N,N-dimethylacetamide may be used for preparing the solvates. In particular, 1.5 moles of N-methylpyrrolidone, or 0.75 moles of N,N-dimethylacetamide may be added per mole of cefprozil used. The volumes of N-methylpyrrolidone, or N,N-dimethylacetamide may be added in an amount ranging from one to 10 times the volume of the solution of cefprozil. For example, three to six volumes of N-methylpyrrolidone, or N,N-dimethylacetamide may be used.

The solvents for preparing the solvates may be any water miscible organic solvents in admixture with water. Examples of suitable solvents include ketones such as acetone and ethylmethyl ketone; acetonitrile; alcohols, such as methanol, ethanol, propanol, and isopropanol; cyclic ethers, such as dioxane and tetrahydrofuran; and mixture(s) thereof.

The cefprozil or its salts can be obtained by methods known in the art including those described in U.S. Patent Nos. 4,520,022; 4,727,070; 5,608,055; 6,060,268; 6333409, and 2002/120136. In particular, it was prepared according to our co-pending PCT Patent Application Serial Nos. PCT/IB03/04439, and PCT/IB2004/000850. The starting cefprozil may be obtained as a solution directly from the reaction in which cefprozil is formed, for example as disclosed in the patents/ patent applications listed above, and used as such without isolation.

Generally, the solvate precipitates out of the solution or the reaction mixture spontaneously. The precipitation may also be facilitated by adding seeds of the solvate. The precipitation may also be induced by reducing the temperature.

The precipitated solvate may be isolated by conventional methods such as filtration, filtration under vacuum, decantation or centrifugation.

The product obtained may be further or additionally dried. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

In another aspect, the N-methylpyrrolidone or N,N-dimethylacetamide solvates of cefprozil are converted to crystalline cefprozil. In general, the crystalline cefprozil is prepared by obtaining a solution of N-methylpyrrolidone solvate or N,N-dimethylacetamide solvate of cefprozil in one or more solvents; stirring the solution at a temperature of from about 20°C to about 60°C; and isolating the crystalline cefprozil.

The solvents may be any water miscible organic solvents in admixture with water. Examples of suitable solvents include ketones such as acetone and ethylmethyl ketone; acetonitrile; alcohols, such as methanol, ethanol, propanol, and isopropanol; cyclic ethers, such as dioxane and tetrahydrofuran; and mixture(s) thereof.

The crystalline cefprozil product may be obtained as a monohydrate or a hemihydrate of cefprozil. The conversion of the solvates to crystalline cefprozil in the desired form may be facilitated by adding seeds of the desired form of crystalline cefprozil or by reducing the temperature.

The crystalline cefprozil obtained may be isolated by conventional methods such as filtration, filtration under vacuum, decantation or centrifugation.

The product obtained may be further or additionally dried. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

The resulting crystalline cefprozil may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the

medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and are not intended to limit the scope of the invention. Although the examples are directed to the mono N, N-dimethylacetamide solvate and N-methylpyrrolidone monohydrate solvates of cefprozil, and crystalline cefprozil, the principles described in these examples can be applied to other solvates of cefprozil.

Methods

X-ray Powder Diffraction

X-ray powder diffraction patterns were recorded using the following instrument and parameters:

X-Ray Difractometer, Rigaku Coorperation, RU-H3R

Goniometer CN2155A3

X-Ray tube with Cu target anode

Divergence slits 1°, Receiving slit 0.15mm, Scatter slit 1°

Power: 40 KV, 100 mA

Scanning speed: 2 deg/min, step: 0.02 deg

Wave length: 1.5406 A

Infrared Spectra

Infrared spectra were recorded using the following instrument and parameters:

Instrument: Perkin Elmer, 16 PC

SCAN: 16 scans, 4.0 cm^{-1}

According to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

The NMR spectra were obtained on a Bruker (DRX 300) 300 MHz instrument. The chemical shifts are expressed in ppm values (parts per million downfield from tetramethylsilane).

In conjunction with the NMR spectra, the following abbreviations are used: "s" is singlet, "d" is doublet, "t" is triplet, "q" is quartet, and "m" is multiplet.

Example 1

Preparation of 7[(D)-2-amino-2-(4-hydroxyphenyl) acetamido]-3-(Z/E)-1-propenyl]-ceph-3-em-4-carboxylic acid (cefprozil), N,N-dimethylacetamide solvate (2:1.5)

Solution A - To a stirred slurry of 7 amino-3-[(Z/E)-1-propen-1-yl]-cephe-3-em-4-carboxylic acid (7-APCA, 100 g) in methylene chloride (500ml) were added hexamethyldisilazane (50g), trimethylchlorosilane (35g) and imidazole(1.0g). The reaction mixture was refluxed for 4 hours and then cooled to -10 °C.

Solution B - Potassium (D)-N-[1-methoxycarbonyl propen-2-yl]- α-amino-p-hydroxyphenylacetate (dane salt, 141g) was stirred in methylene chloride (600ml). N,N - dimethylacetamide (DMAc, 400ml) was added and the slurry was stirred at -35 to - 40°C. N-methylmorpholine(0.8g) and ethylchloroformate(56.5g) were added, the mixture stirred for 1.5 hours at –35 to -40°C and then cooled to -65°C.

The solution A was added into the solution B at -65°C and stirred for 1 hour at -40 C. The temperature was raised to -30 to -25°C and further stirred for 1.5 hours. A mixture of water (350 ml) and hydrochloric acid (35%, 75ml) was added to the reaction mixture and stirred for 15 minutes at 0 to 5 °C. The aqueous layer was separated. Dimethylacetamide (1500ml) and acetone (300 ml) were added to the aqueous layer. pH of mixture was adjusted to 6.0 with ammonia solution (25%) and stirred for 2.0 hours at 20-25°C. The solid obtained was filtered and washed with dimethylacetamide (200ml) followed by washing with acetone. After drying at 40°C, 150g of the title solvate was obtained.

Moisture content (by KF) =0.7% w/w

^{1}H-NMR (D_2O-DCl), δ(ppm): 7.4 (d, 2H), 6.94 (d, 2H), 5.97(d, 1H), 5.71-5.78 (m, 1H), 5.66 (d, 1H), 5.0-5.13 (d, 2H), 3.29-3.48 (m, 2H), 3.20 (s, 2H), 2.91(s, 2H), 2.09 (s, 2H), 1.53-1.55 (d, 3H).

IR in KBr pellet (cm^{-1}) – 3422, 3217, 3025, 1764, 1697, 1558, 1518, 1400, 1349, and 1263.

X-Ray Powder Diffraction Pattern:

d-value (°A)	2θ (°)	I/Io %
13.63	6.48	100
12.47	7.08	87
10.44	8.46	73
10.15	8.70	64
6.65	13.30	30
6.32	14.00	30
4.84	18.32	54
4.72	18.78	93
4.42	20.06	57
4.29	20.70	48
4.17	21.28	47
4.10	21.64	62
4.01	22.16	53
3.91	22.72	43
3.60	24.70	42
3.42	26.00	40
3.35	26.58	38

Example 2

Preparation of 7[(D)-2-amino-2-(4-hydroxyphenyl) acetamido]-3-(Z/E)-1-propenyl]-ceph-3-em-4-carboxylic acid (cefprozil), N-Methyl-2-pyrrolidone solvate (1:1.5)

7-APCA (50g) was reacted according to the procedure described in Example 1 using N-methyl-2-pyrrolidone instead of dimethylformamide to obtain 76g of the title solvate.

^{1}H-NMR (D_2O-DCl), δ(ppm): 7.2-7.25(d, 2H), 6.80-6.83(d, 2H), 5.87-5.91 (d, 1H), 5.61-5.68(m, 1H), 5.54-5.55(d, 1H), 5.02-5.03(d, 2H), 3.12-3.34(m, 2H), 2.6-2.7(s, 3H), 2.29-2.35(t, 2H), 1.94-1.84(m, 2H), 1.42-1.45(d, 3H).

IR in KBr pellet (cm^{-1}) – 3420, 3216, 3028, 1779, 1699, 1667, 1567, 1518, 1448, 1400, and 1350.

X-Ray Powder Diffraction Pattern:

d-value (°A)	2θ (°)	I/Io %
14.15	6.24	99
13.63	6.48	96
5.05	17.54	26
4.75	18.64	100
4.59	19.30	44
4.51	19.66	33
4.43	20.02	40
4.18	21.22	31
4.06	21.86	44
3.60	24.74	31
3.32	26.80	27

Example 3

Preparation of Crystalline Cefprozil Monohydrate

Cefprozil dimethylacetamide solvate (100g) prepared in Example 2 was stirred in water (200ml) at 40-45°C for 120minutes. It was then cooled to 5-8°C and filtered to obtain crystalline cefprozil monohydrate.

Yield: 74.0g

Moisture content (by KF) =4.5% w/w

HPLC (Assay) – 100.1% on dry basis.

Example 4

Preparation of Crystalline cefprozil monohydrate

Cefprozil N-methyl-2-pyrrolidone solvate (50g) as prepared in Example 3 was stirred in water (150ml) at 45-50°C for 120 minutes. The mixture was cooled to 0-5°C and crystalline cefprozil monohydrate was collected by filtration.

Yield: 35g

Moisture content (by KF) =4.8% w/w

HPLC (Assay) – 99.8% on dried basis.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.